REMARKS

Claims 15-42 are currently pending. Claims 1-14 and 17 are canceled without prejudice or disclaimer. Claims 19-21, 25, 28-34 are indicated as withdrawn. Applicants reserve the right to pursue the subject matter of any canceled or withdrawn claims in one or more continuing applications. Furthermore, by electing restricted subject matter with traverse in their response to Restriction Requirement filed September 24, 2007, Applicants have preserved their right to file a petition regarding the inappropriate restriction of claimed subject matter. Currently claims 15, 16, 18, 22-24, 26, 27 and 35 have been examined.

Claims 15, 16, 18, 23, 24, 26, 27 and 35 are amended. Support for the amendments to each of these claims can be found in the claims and specification as originally filed. In particular, support for the amendments to claim 15 can be found at claim 15 as originally filed, the specification at paragraphs [0010], [0012], [0014] and [0020] as well as elsewhere throughout the specification as originally filed. Claims 16, 23, 24, 26, 27 and 35 are amended to maintain consistency with the amendments to independent claim 15. As requested by the Examiner, claim 18 is amended to insert "full names" of the poison proteins listed therein. Accordingly, the current amendments do not constitute the addition of new matter.

Claims 41 and 42 are new. Support for these new claims can be found in the specification as originally filed. In particular, claims 41 and 42 are supported by paragraphs [0016]-[0022] and elsewhere throughout the specification. Accordingly, the new claims do not add matter to the application.

Priority

The Examiner asserts that claim 27 is not supported by U.S. Provisional Patent Application No. 60/365,938 (the '938 application), the priority document for the instant application. Furthermore, the Examiner asserts that a certified copy of application PCT/BE03/00045 (the '045 application), which corresponds to the instant application, has not been filed, and thus, it cannot be determined if claim 27 is supported by the specification.

Applicants submit that claim 27 is supported by both the '938 application and the '045 application. With respect to the '938 application, Applicants would like to draw the Examiner's attention to the last sentence of page 4. With respect to the '045 application, Applicants would

like to point out that upon entry of the U.S. national phase, they filed a copy of the publication of the '045 application (WO03/078638) as the specification. Applicants do not believe that the rules require that they provide a certified copy of the specification. If any doubt remains as to where support can be found for claim 27 in the application as filed, Applicants invite the Examiner to review paragraph [0046] of WO03/078638, which is the specification as published by WIPO.

Claim Objections

The Examiner objects to claim 18 as lacking the complete names for the poison proteins set forth therein. In particular, the Examiner alleges that a full name is required and that each of the genes should be set out in parentheses after the full name.

Applicants have amended claim 18 as requested by the Examiner. Applicants would like to point out that MazF has no full name. The name MazF was named in sequence after the MazE gene. The name MazE is derived from the Hebrew words "ma-ze," which mean "what is it" (see, Metzger et al. (1988) *J Biol. Chem.* **263**: 15699-704, a copy of which is provided herewith for the Examiner's convenience).

Although Applicants have complied with the Examiner's request, it is submitted that such amendment should not be required since those of ordinary skill in the art identify and refer to the listed poison proteins by the abbreviated name rather than the full name. In fact, the full names of most, if not all, of the poison proteins recited in claim 18 are not known by those skilled in the art and would be virtually useless as an identifier in the absence of the abbreviated name.

In view of the foregoing amendment, Applicants request that the Examiner withdrawn the objection to claim 18.

Overview of the claimed subject matter

Prior to discussing the claim rejections, Applicants believe that it would be helpful to briefly discuss the nature of the claimed subject matter. A close examination of independent claim 15 reveals that it is drawn to "[a] recombinant eucaryote cell comprising a genetic construct incorporated at a specific site in the genome of said cell, said genetic construct comprising a genetic sequence encoding a poison protein selected from a poison/antidote group,

wherein said genetic sequence is under the control of an inducible promoter/operator, and wherein said poison protein is toxic to said cell; and a genetic sequence encoding an antidote molecule to said poison protein with the condition that the sequence encoding the antidote molecule is not native to said cell." Thus, claim 15 relates to a recombinant cell having a sequence encoding a poison protein integrated in the cell's genome, wherein expression of the poison protein can be regulated. The cell also comprises a sequence encoding an antidote molecule that suppresses the toxic effect of the poison protein. As such, the cell can survive when the poison protein is expressed provided that the antidote protein is present in the cell at levels sufficient to overcome the toxic effect of the poison protein. If the amount of poison protein expression is increased so as to overcome the suppressive effect of the antidote protein or if the level of antidote protein is reduced such that is becomes ineffective at suppressing the poison protein, the cell will die.

Cells engineered with such a poison/antidote system can serve as a host strain which permits the following: (i) the integration of one or more exogenous DNA sequences into the genome of the cell at a specific location; and (ii) the selection of cells which have undergone such an integration event. When the cells are propagated prior to transfection with an exogenous nucleic acid sequence, expression of the poison protein is down regulated and expression of antidote protein is up regulated to negate the effects of any basal or "leaky" expression of the poison protein. Such cells can then be transfected with an exogenous nucleic acid sequence that is to be integrated into the genome. After sufficient time is permitted for the exogenous sequence to integrate, the promoter controlling the expression of sequence encoding the poison protein is up regulated and the level of antidote protein is reduced in the cell to a level insufficient to overcome the toxic effect of poison protein produced by the cell. If integration occurs at the site containing the poison protein (the specific location) expression of the poison protein will be eliminated. Non-integration of the exogenous sequence, or integration of the exogenous sequence at any other location in the genome, will not inactivate the expression of the poison protein. Thus, cells that have not undergone the specific integration event so as to eliminate the expression of the poison protein will continue to express the poison protein and die. In contrast, cells that have undergone the specific integration event so as to eliminate the expression of the poison protein will not express the poison protein, and thus, such cells will survive the selection

process. Accordingly, the novel and inventive subject matter of this claim is a recombinant eucaryote cell having a combination of introduced genetic elements that permits both the integration of an exogenously introduced sequence at a specific genomic location and the selection of cells containing the integrated sequence.

Rejection of claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 101

The Examiner rejects claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 101 as allegedly lacking utility. In particular, the Examiner asserts that the invention set forth in the claims "is not supported by either a specific or substantial utility" (see page 5 of the instant Office Action). Later, at page 6 of the instant Office Action, the Examiner further asserts that the specification does not set forth a credible utility. The arguments that the Examiner presents in support of the utility rejection appear to be that: (i) the claims encompass at least 1.6 million species of eucaryotes and that no specific utility has been established for each of those species; and (ii) "the claimed genetically modified eukaryotes are just invitations for one skilled in the art to figure out how a gene of interest functions or what the biological activities are for the claimed invention." The Examiner also seems to argue that "the instant application has failed to provide guidance as to the identity of all of the toxic genes and their corresponding antidote genes embraced by the generic claim, and how one of skill in the art could use the claimed invention of nucleic acids in a way that constitutes a credible, specific and substantial utility."

Applicants do not agree that the subject matter of any of claims 15, 16, 18, 22-24, 26, 27 or 35 lacks utility. A claimed invention possesses utility if the Applicant asserts a specific and substantial use that is viewed a credible by one of ordinary skill in the art or if "a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention." MPEP § 2107. Furthermore, "[a]n applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement." *Id.* Moreover, "[o]ffice personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement." *Id.* Although Applicants submit that a skilled artisan would acknowledge a well established utility for the invention by simply reading

independent claim 15, Applicants would also like to point out the specification is replete with statements of specific and substantial utility that are credible. For example, the specification at paragraph [0010] states that:

> The present invention is based upon a method and a poison/antidote genetic system used for the selection of stable insertion of foreigner (exogenous) DNA fragment(s) into the genome of an eucaryote cell or a pluricellular organism but which allows also the precise targeting of said insertion in a specific (preferably predefined) location in said genome and the possibility to easily characterize the presence, the integrity and the correct orientation of said inserted foreigner (exogenous) DNA fragment(s) into the genome of said cell or organism.

It is clear that this statement of utility is both specific and substantial since recombinant eucaryote cell that permits precise targeting of an exogenous sequence to the genome of the cell and insertion of that exogenous sequence into the genome at a specific location is desirable by those of ordinary skill in the art. As described in the specification, such cell systems represent a substantial improvement over systems currently available that only permit random insertion of exogenous sequences into the genome at low frequency (see paragraphs [0006] and [0007] of the instant specification). Furthermore, such cell systems are improved because they avoid integration of multiple copies of the same sequence in unspecified locations in the genome. This eliminates the risk that one or more important genomic sequences become inactivated upon integration of the exogenous sequence.

The statement of utility is credible for at least several reasons. For example, the specification provides detailed instructions as to how to make such recombinant cells and how to use such cells for site specific integration of an exogenous nucleic acid sequence. These instructions can be readily understood by those of ordinary skill in the art. The Examiner has not identified any statements regarding the preparation or use of such cells that a skilled artisan would not find credible. Even if we were to assume, *arguendo*, that the Examiner did identify such statements, the Examiner has not met the burden of providing "countervailing evidence . . .

that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement" as set forth in section 2107 of the MPEP.

With regard to the Examiner's assertion that the claims encompass at least 1.6 million species of eucaryotes and that no specific utility has been established for each of those species, Applicants submit that the utility requirement has no provision requiring that Applicants make individual statements of utility for each of the 1.6 million species allegedly covered by claim 1. In fact, it is well established that "[a]n applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement." MPEP § 2107.

Regarding the Examiner's statement that "the claimed genetically modified eukaryotes are just invitations for one skilled in the art to figure out how a gene of interest functions or what the biological activities are for the claimed invention," Applicants fail to see its relevancy with respect to the utility of the claimed subject matter. As previously discussed, the claimed invention relates to a novel system for integrating an exogenous sequence into the genome of a eucaryote cell at a specific location. The exogenous sequences subsequently transfected into the cell can have a known function or an unknown function. Describing the system as only for use in the expression and/or screening of genes of unknown function is quite an artificial and unreasonable limitation on the claims as written. Yet even if we assume, *arguendo*, that the claims were limited as the Examiner asserts, such recombinant cells would be useful in their own right as a tool for screening the effects of unknown genes on the host eucaryote cell types. Nevertheless, it is clear that the claimed invention has much broader application. For example, the invention would permit one or more sequences having known function to be integrated into the cell genome so as to create an engineered cell line useful for conducting the biological process mediated by those genes (e.g., a biotransformation).

Finally, with respect to the Examiner's assertion that "the instant application has failed to provide guidance as to the identity of all of the toxic genes and their corresponding antidote genes embraced by the generic claim, and how one of skill in the art could use the claimed invention of nucleic acids in a way that constitutes a credible, specific and substantial utility," Applicants again submit that the establishing utility does not require that Applicants list all of the toxic genes that could be used in the instant invention. It should be noted, however, that claim

15 does state that the poison protein is selected from a poison/antidote group and that the specification lists most, if not all, of the known poison/antidote systems.

In view of the foregoing remarks, Applicants submit that one of skill in the art would readily recognize several specific and substantial utilities that are credible for the invention as claimed. Accordingly, Applicants request that the Examiner withdraw the rejection of claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 101.

Rejection of claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 112, first paragraph (enablement)

The Examiner asserts that a rejection under 35 U.S.C. § 101 must be accompanied by a rejection under 35 U.S.C. § 112, first paragraph because a skilled artisan would not know how to use claimed subject matter that lacks utility.

Applicants submit that the above arguments overcome the rejection under 35 U.S.C. § 101. Because the Examiner has provided no reasons other than the alleged lack of utility as to why a skilled artisan would not know how to use the claimed subject matter, Applicants submit that overcoming the rejection under 35 U.S.C. § 101 obviates the instant rejection under 35 U.S.C. § 112, first paragraph.

In view of the remarks above, Applicants request that the Examiner withdraw the above enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection of claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejects claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 112, first paragraph as allegedly lacking adequate support by the specification. In particular, the Examiner asserts that the specification does not disclose a representative number of genes encoding toxic proteins or a representative number of genes encoding antidotes. The Examiner further asserts, without any support, that the each of these groups "embraces an enormous genus of structurally distinct and undisclosed molecules." Additionally, the Examiner asserts that applicants have not provided sufficient support for making non-human transgenic organisms having the genetic construct recited in claim 15.

Applicants maintain that each of claims 15, 16, 18, 22-24, 26, 27 and 35 are fully supported by the instant specification. Although these claims are currently amended, Applicants maintain that each of these claims was supported prior to the instant amendments. With respect to the Examiner's contention that the specification lacks a representative number of examples of poison/antidote systems, Applicants would like to point out the following items. First, claim 15 recites, in relevant part, that the cell comprises "a genetic sequence encoding a poison protein selected from a poison/antidote group" and "a genetic sequence encoding an antidote molecule to said poison protein." Thus, the genus of sequences encoding poison proteins is limited to those sequences encoding poison proteins from a poison/antidote group. Similarly, the genus of sequences encoding antidote molecules is limited those from a poison/antidote group. Contrary to the Examiners assertion regarding the enormity of such groups, poison/antidote systems fall into a limited number of systems that are well established in the art (see, Kielenkiewicz et al. (2001) *Acta Biochimica Polonica.* **48(4)**: 1003-1023, a copy of which is provided herewith for the Examiner's convenience). As demonstrated by the Examiner, the specification at paragraphs [0023] and [0024] lists most of the poison/antidote pairs known at the time of filing the instant application. Furthermore, even if the specification does not literally list every antidote corresponding to every particular poison protein, as the Examiner alleges is the case for ParE, RelE and MazE, it was well known in the art at the time of filing the instant application that the partners for each of these proteins are ParD, RelB and MazF, respectively. If the Examiner still believes that the genus of poison/antidote systems is enormous and that Applicants have not described a representative number of such systems, the Examiner is invited to provide some evidence as to the alleged enormity of this genus as well as why Applicants' disclosure of most of the known systems is not representative of the genus.

With respect to the assertion that the specification does not provide support for regenerating organisms from totipotent cells containing the genetic construct recited in independent claim 15, Applicants submit that the claims have been amended to remove the term "organism." Applicants have made this amendment solely to expedite the allowance of the claims and do not concede that the specification does not adequately support this specific limitation.

In view of the foregoing remarks and amendments, Applicants request that the Examiner withdraw the above rejection of claim 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 112, first paragraph.

Further rejection of claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 112, first paragraph (enablement)

In addition to the above enablement rejection issued in connection with the utility rejection, the Examiner further rejects claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 112, first paragraph a not being enabled by the specification. In particular, the Examiner asserts that, in view of the teachings of the instant specification, a skilled artisan would require undue experimentation to make and use the claimed subject matter. The Examiner goes on to assert Applicants disclose no examples other than the disclosure of a mutation in the nucleic acid sequence encoding GyrA that would render a host cell resistant to the toxic effect of CcdB. Furthermore, the Examiner asserts that the targets of some of the listed poison proteins are not known and that a skilled artisan would require undue experimentation to discover such targets. In addition, the Examiner alleges that Applicants' examples do not enable the use of the full scope of available poison/antidote systems. The Examiner also seems to assert that Applicants have not enabled making and using the claimed cells and organisms.

Applicants maintain that claims 15, 16, 18, 22-24, 26, 27 and 35 are fully enabled by the specification. The genetic elements and methods necessary for making the subject matter recited in the above-rejected claims is disclosed in the specification as filed. For example, the nucleic acid sequences encoding most of the known poison/antidote systems are described in the specification (see the instant specification at paragraphs [0023] and [0024]). The specification also describes promoters that regulate gene expression in eucaryote cells (see the instant specification at paragraphs [0035] and [0038]). Furthermore, many such promoters are well known in the art. Methods for integrating the promoter-controlled genetic sequence encoding the poison protein into the genome of the eucaryote host cell and selecting for cells containing such integrants are described in the specification at paragraphs [0012]-[0018]. Methods for introducing a genetic sequence encoding an antidote to the poison protein into the eucaryote cell

are also known. Accordingly, no undue experimentation is required to make recombinant cells set forth in independent claim 15.

The Examiner's comment regarding whether the target of a particular poison protein is known in the art is irrelevant to the claimed subject matter. The only information required by the skilled artisan is the sequence encoding the poison protein and the sequence encoding the antidote. Although modification of the target of a poison protein is a supplemental or an alternative means by which a cell may be rescued from the effect of the poison protein (as exemplified in the specification by the *gyr*A mutation), modification of the target is not a necessary element for implementing the claimed subject matter because the toxic effect of the poison protein can be negated by expression of the known antidote protein. Thus, to implement the claimed subject matter, a skilled artisan requires absolutely no knowledge regarding the target of the poison protein.

With respect to the applicability of poison/antidote systems to eucaryote cells and organisms, Applicants submit that there are numerous reports of the described poison/antidote systems functioning in eucaryotes (for example, see Kristoffersen et al. (2000). *Appl. Environ. Microbiol.* **66**: 5524-26 and Yamamoto et al. (2002) *FEBS Letters* **519**: 191-4, copies of which are attached for the Examiner's convenience). Even if not every poison/antidote system is functional in every eucaryote cell, this does not render the claim non-enabled. It is well established that "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled" MPEP §2164.08. Furthermore, one of ordinary skill in the art can easily determine whether expression of a poison protein kills a eucaryote cell and whether expression of the antidote rescues the cell using routine methods. Accordingly, inoperable embodiments covered by claim 15, if any, can easily be identified without any undue experimentation.

With respect to the assertion that the specification does not enable production of transgenic organisms from totipotent cells containing the genetic construct recited in independent claim 15, Applicants submit that the claims have been amended to remove the term "organism." Applicants have made this amendment solely to expedite the allowance of the claims and do not concede that the specification does not enable construction of such organisms.

In view of the foregoing remarks and amendments, Applicants request that the Examiner withdraw the above rejection of claim 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 112, first paragraph.

Rejection of claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 112, second paragraph as allegedly indefinite. In particular, the Examiner asserts that the use of the phrase "its genome" in claim 15 leads to a lack of clarity. Additionally, the Examiner asserts that the phrase "a poison protein selected from a poison/antidote group" in claim 15 is unclear. Finally, the Examiner asserts that the phrase "not natively present" in claim 15 is not defined.

Applicants submit that claims 15, 16, 18, 22-24, 26, 27 and 35 are clear as written. Although claim 15 has been amended, Applicants submit that this claim complied with the requirements of 35 U.S.C. § 112, second paragraph prior to the amendment. Nevertheless, the amendment to claim 15 renders the first of the above-listed indefiniteness rejections moot.

With respect to the second of the above-listed indefiniteness rejections, Applicants submit that, in view of the specification, and in particular paragraphs [0023], [0024] and [0027], a skilled artisan would readily recognize that the phrase "a poison protein selected from a poison/antidote group" means "a poison protein selected from a set of proteins comprising poison/antidote protein pairs. The alternative construction proposed by the Examiner at page 18 of the instant Office Action does not make sense, and thus, would cause a skilled artisan no confusion, especially in view of the specification. Also at page 18 of the instant Office Action, the Examiner seems to suggest that claim 15 requires a listing of each species of poison and antidote protein. Applicants cannot agree. As stated above, in view of the specification, a skilled artisan would clearly understand what is meant by "a poison protein," "an antidote molecule to said poison protein" and a "poison/antidote group." Listing a particular species of poison protein and antidote protein would unduly narrow the claim without any improvement to claim clarity.

With respect to the third of the above-listed indefiniteness rejections, Applicants submit that the phrase "not natively present" is clear on its face. According to the Merriam Webster's dictionary, "natively" means "indigenously" and the term "indigenous" means occurring naturally in a particular environment. Thus, "an antidote molecule not present natively in said

cell" would clearly be an antidote molecule that does not naturally occur in the cell. By way of amendment, Applicants changed the phrase "not present natively in said cell" to "not native to said cell." Applicants submit that both the original and the amended language would be understood by a skilled artisan to mean not naturally occurring in the cell (i.e., exogenously introduced).

In view of the foregoing remarks, Applicants request that the Examiner withdraw the above rejection of claim 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 112, second paragraph.

Rejection of claims 15, 16, 18, 22-24, 26 and 35 under 35 U.S.C. § 102(a) and (e)

The Examiner rejects claims 15, 16, 18, 22-24, 26 and 35 under 35 U.S.C. § 102(a) and (e) as allegedly anticipated by U.S. Patent No. 6,271,359 (Norris et al.). In particular, the Examiner asserts that Norris et al. disclose every element of each of the above-rejected claims. Applicants do not agree.

Applicants submit that claims 15, 16, 18, 22-24, 26 and 35 are not anticipated by Norris et al. In particular, Norris et al. fail to disclose a genetic construct incorporated in the genome of a cell as recited in independent claim 15. Furthermore, Norris et al. fail to disclose that the genetic construct is incorporated at a specific site in the genome. It is well settled that an anticipatory reference must expressly or inherently disclose each and every element of a claim. The test for inherent disclosure is narrow and requires that the inherent feature must be a "necessary and inevitable" consequence of the disclosure. *Schering Corp. v. Geneva Pharmaceuticals, Inc.,* 339 F. 3d 1373, 1375 (Fed. Cir. 2003). Independent claim 15 recites, "[a] recombinant eucaryote cell comprising a genetic construct incorporated at a specific site in the genome of said cell, said genetic construct comprising a genetic sequence encoding a poison protein selected from a poison/antidote group, wherein said genetic sequence is under the control of an inducible promoter/operator and, wherein said poison protein is toxic to said cell; and a genetic sequence encoding an antidote molecule to said poison protein with the condition that the sequence encoding the antidote molecule is not native to said cell." As such, Norris et al. must either explicitly disclose the claimed compositions in their entireties or they must provide an inherent disclosure of those compositions. Norris et al. does not provide any disclosure of a

eucaryote cell having a genetic construct incorporated at a specific site in the genome of said cell. The Examiner asserts that Norris et al. disclose delivering a sequence encoding a toxic molecule to a target cell using a vector that may be capable of integrating into the genome. It must be recognized, however, that integration of a nucleic acid construct into the genome of a cell is not a necessary and inevitable consequence of delivering a nucleic acid construct to a cell via an vector that may be capable of integration. Furthermore, claim 15 has been amended to recite, in relevant part, that the genetic construct is incorporated at a specific site in the genome of said cell. Norris et al. do not disclose integration at a specific site. Accordingly, Norris et al. do not literally or inherently disclose the cells set forth in any of the instant claims.

Rejection of claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 103(a)

The Examiner rejects claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 103(a) as allegedly obvious over Kristoffersen et al. in view of Parekh et al. Furthermore, the Examiner rejects claims 15 and 18 as allegedly obvious over the combination of Kristoffersen et al. and Parekh et al. in view of Norris et al. Finally, the Examiner rejects claims 15 and 27 as allegedly obvious over the combination of Kristoffersen et al., Parekh et al and Norris et al. in view of Newman et al. and in further view of Rochaix et al. With respect to claims 15, 16, 22-24, 26 and 35, the Examiner asserts that Kristoffersen et al. disclose introduction of genetic sequences encoding poison and antidote proteins into yeast. The Examiner acknowledges that Kristoffersen et al. do not disclose integration of the sequence encoding the poison protein into the yeast genome. The Examiner, however, asserts that Parekh et al. disclose yeast integrative vectors. The Examiner then contends that a skilled artisan would be motivated to combine the integrative vectors of Parekh et al. because the integrative vector would be stably propagated to progeny cells. The Examiner also contends that there would be a reasonable chance of success because such as substitution allegedly would lead to results predictable to those of ordinary skill in the art. With respect to claims 15 and 18, the Examiner alleges that Norris et al. disclose the additional element of using CcdB/CcdA as a poison/antidote system, that a skilled artisan would be motivated to use such a system in place of RelE/RelB in order to optimize the transformation and stable propagation of the transformation vector, and that a simple substitution of these known elements would yield predictable results. Finally, with respect to claims 15 and 27, the

Examiner asserts that Newman et al. disclose the additional element of using a chloroplast integrating transformation vector, that a skilled artisan would be motivated to use such a vector in place of the nuclear integrating vector allegedly disclosed by Parekh et al. in order to optimize the transformation and stable propagation of the transformation vector, and that a simple substitution of these known elements would yield predictable results.

Applicants submit that claims 15, 16, 18, 22-24, 26, 27 and 35 are not obvious over any of the combinations of the above-cited references. Claim 15 has been amended to recite, in relevant part, that the genetic construct is incorporated at a specific site in the genome of said cell. As acknowledged by the Examiner, Kristoffersen et al. do not disclose integrative vectors. The vectors disclosed by Parekh et al. produce multiple integrations which are not at a specific site. As such, the combination of Kristoffersen et al and Parekh et al. do not disclose all of the elements of independent claim 15 or any of the claims dependent thereon. None of the references Norris et al., Newman et al. or Rochaix et al. remedy this defect. Accordingly, no combination of references cited by the Examiner disclose all of the elements of the claims.

In addition to lacking all of the necessary elements of the claimed invention, a skilled artisan would not be motivated to combine the disclosure of Kristoffersen et al. with that of Parekh et al. Kristoffersen et al. relate to biological containment systems and does not suggest that integration of the poison protein would improve such systems. Parekh et al. relates only to integrative vectors for use with yeast. The Examiner contends that a skilled artisan would want to increase the effectiveness of the system disclosed by Kristoffersen et al. by integrating the sequence encoding the poison protein into the genome of the cell. Applicants, however, do not agree that integrating a sequence encoding a poison protein into the cell would improve the biological containment system disclosed by Kristoffersen et al. In fact, integration of a sequence encoding a poison protein into a host cell genome would prevent the elimination of the containment system when it is no longer desired or necessary. As such, the skilled artisan would not be motivated to modify the disclosure of Kristoffersen et al. in view of Parekh et al.

In addition to the foregoing remarks, Applicants submit that it is only through hindsight analysis that the Examiner applies the disclosure of Parekh et al. to that of Kristoffersen et al. The instant invention is a novel recombinant eucaryote cell that opens a new field of technology of genetic engineering for eucaryote cells. This recombinant cell is capable of receiving an

exogenous nucleic acid sequence into its genome at a specific location. The invention overcomes known problems in the art with achieving site specific integration and selecting for low frequency integration events by placing a poison cassette at a specific location in the genome. Furthermore, the cells claimed herein do not allow integration of multiple copies of the same sequence in unspecified locations in the genome. In addition, because the integration is at a specific site in the genome, there is no risk that one or more important genomic sequences become inactivated upon integration of the exogenous sequence. It should be kept in mind that an invention is not deemed obvious simply because most or all of the elements can be found separately in the art. Without the benefit of the instant specification, a skilled artisan would not have combined the elements of the instant invention so as to create the claimed eucaryote cell type which has a genetic construct for receiving an exogenous nucleic acid sequence into its genome at a specific location.

In view of the foregoing remarks and amendments, Applicants respectfully request that the Examiner withdraw the rejection of claims 15, 16, 18, 22-24, 26, 27 and 35 under 35 U.S.C. § 103(a).

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Co-Pending Applications of Assignee

Applicant wishes to draw the Examiner's attention to the following co-pending applications of the present application's assignee.

Serial Number	Title	Filed
10/168,774	DOUBLE SELECTION VECTOR	06/20/2002
10/526,525	REVERSIBLE, PARALLEL AND MULTITASK CLONING METHOD AND KIT	08/26/2005
11/558,856	CYTOTOXIN-BASED BIOLOGICAL CONTAINMENT	11/10/2006
11/837,456	CYTOTOXIN-BASED BIOLOGICAL CONTAINMENT	08/10/2007

CONCLUSION

Applicants believe that all outstanding issues in this case have been resolved and that the present claims are in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to contact the undersigned at the telephone number provided below in order to expedite the resolution of such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 10, 2008

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